REMARKS

Claims 5-11 are active and are drawn to the elected subject matter.

Claim 5 is amended to insert the full name of APP and Claim 11 is amended to include a period. No new matter or new issues arise that preclude entry of these amended claims even though presented after a final rejection.

Applicants thank Examiner Kolker for the courtesy of discussing this case with their undersigned representative on October 21, 2009. During this meeting, the 103 based rejections citing to DeMattos and Sen and further in view of Boos were discussed. The details of this discussion are provided in the remarks below that also address the applied rejections.

The rejection concedes that DeMattos et al. teaches using antibodies against Aβ delivered to a patient to remove this protein from the brain and into the blood so that Aβ is significantly increased in the blood stream. DeMattos et al. further hypothesize "that peripherally administering the antibody alters the equilibrium of Aβ between brain and plasma, suggesting that after circulating Aβ is sequestered in the blood, more Aβ exists in the brain."

The rejections also clearly concede that DeMattos et al. do not teach contacting the blood or plasma flow of a patient with an apheresis device that has the anti-Aβ antibodies attached to the surface of a solid carrier (see page 3 3rd paragraph, last sentence of the Office Action). The examiner's wording (does not explicitly teach) could be interpreted as if he assumes that DeMaffos et al. could implicitly teach such a step. This, however, is erroneous. Conclusions of obviousness based on clearly erroneous findings, as is here the case, cannot stand. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006).

The rejection cites Sen et al. to allege that an immunoaffinity column described in this article is an apheresis device according to the present invention. Although this is incorrect, the examiner then further argues that "Sen does not teach contacting blood or plasma flow from patients with AD with the device" (see page 4, 1 paragraph, last sentence).

Reference is made to Boos et al. disclosing a specific apheresis device.

Applicants respectfully submit that the rejections fail to make out a *prima facie* case of obviousness. That is, DeMattos, the main citation for Aβ, clearly teaches removing Aβ from the brain into the blood by introducing antibodies into the patient whereas the present method does not introduce that into the patient nor seeks to put more Aβ in the blood. Rather, the present method seeks to remove Aβ from the blood, in direct contrast to DeMattos's goal.

DeMattos et al. disclose a passive immunisation wherein an Aβ antibody is administered to a patient. This completely differs from the present invention, where any contact of the antibody with the patient is to be prevented. This is safeguarded according to the present invention by immobilizing the antibody in an extracorporal circulation device and lowering the amount of Aβ present in blood by this apheresis. Again, in contrast thereto, DeMattos et al. obtain a significant, up to 1,000-fold increase of A in blood due to the treatment they described. In DeMattos et al. the action of the antibody is an intracorporal action wherein the antibody acts by using the physiological clearance process, it is the presence of the circulating antibody which results in a change in the equilibrium of Aβ between CNS and plasma and not a decrease in plasma A as in the present invention (see DeMattos, page 8853, 1 paragraph). The effect of the DeMattos et al. treatment is therefore based on the net increase in plasma Aβ whereas the treatment according to the present invention results in a decrease of plasma Aβ.

According to DeMattos et al. an intracorporally administered "classical" medicament (an antibody) is used and that this medicament exhibits its action inside the body of the patient, whereas according to the present invention an extracorporal medical device and technique is used for performing the treatment. No pharmaceutically active substance is applied to the patient. Quite in contrast, the Aβ adsorber according to the present invention must not get into the body of the patient (see also page 9, last paragraph to page 10, 1 paragraph of the present specification). With the present invention, the possibility for triggering autoimmune responses (with directly administering the Aβ antibody) is completely prevented and the whole procedure is performed without administration of a medicament at all and without the need to expose the patient to an increase in plasma Aβ.

This shows that the present invention is based on a completely different mechanism which cannot be made obvious by DeMattos et al.. In the present invention apheresis effects a *de novo* clearance by extracorporal Aβ binding whereas according to DeMaffos et al. plasma Aβ is labeled by the administered antibody and this Aβ labeling changes the physiological clearance pathway of Aβ. This is, as stated above, a completely different mechanism.

The article of Sen et al. deals with an immunoaffinity resin. In the present Office Action the examiner notes that the apheresis device according to the present invention has an "expansive definition" (see page 4, 1 paragraph of the present Office Action) and points to page 10 of the present specification. While Applicants understand that, during the prosecution of an application in the Office, claims are to be given their broadest reasonable interpretation consistent with the teaching in the specification (*In re Bond*, 710 F.2d 831, 833 (Fed. Cir. 1990)), it is error to disregard express limitations in the claims. The Examiner may not set up a "strawman" claim and reject it rather than subject matter encompassed by the actual claims.

The plain language of Applicants' claims requires "an apheresis device" (cf Claim 5). The Specification consistently defines the "apheresis device" in the claimed process on page

10 as commercial apheresis apparatuses which can be used in the course of the present invention. Applicants submit that the Examiner erred in broadly interpreting the scope and content of the subject matter claimed in a manner inconsistent with the plain language of the claims and the teaching of the Specification. The immunoaffinity resin as disclosed in Sen et al. which is not used or even usable for the treatment of a patient nor would one with reasonable skill in the art consider it to be an aphersis device.

Finally, the patent of Boos et al. is used for arguing that claim 9 is obvious. Boos et al. disclose sterile pyrogen-free apheresis devices and shows that apheresis columns are known in principle. Of course, the devices described by Boos et al. are applicable in principle in the method according to the present invention, however, the specificities of these devices by Boos et al. (cation/anion exchangers) are completely different in the present invention (anti-APP antibodies). There is nothing in the Boos et al. patent which would render the present invention obvious.

During the aforementioned meeting, it appeared that he Examiner agreed that the rejections are incomplete but provided further comments as to why the rejections were raised initially in the Action. That is DeMattos teaches that anti-Abeta can pull out Abeta from brain into blood and once Abeta is in the blood, it would be desirable to get the Abeta out of the blood for at least two reasons (1) to remove a toxic substance from the body and (2) to avoid excessive Abeta in the blood to sequester the anti-Abeta from pulling out more Abeta out of the brain. The Examiner also acknowledged that Sen is not an aphersis device but is relying on it solely for the purpose that using an antibody affinity column to contact a sample (e.g., blood) and remove a protein is known and the Boos's disclosure makes it known that aphersis devices were known. See also the Examiner's Interview Summary of record in this case.

Applicants respectfully disagree and submit that that the rationale of the obviousness rejectiona is based on hindsight. Where, as here, the rejection of the subject matter Applicants claim is based on hindsight, the rejection is improper. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The arguments can only be made with the knowledge of the invention, not by objective reading of DeMattos. This is also evident by the expression "pulling Aβ out of brain" and completely neglecting the role that the antibody (m266) has been attributed by DeMattos et al.. Also the motivation "to remove toxic Aβ from the body" is not an interpretation according to DeMattos et al.

Again the present invention is not an additional measure to the antibody treatment of DeMattos et al.. It is usable independently of any antibody administration, it uses a completely different way to change an Aβ equilibrium based on completely different kinetics and based on a completely different mechanism resulting in a medical treatment which is completely different from an antibody treatment and which does not bear all the risks associated with antibody treatment. There has been no indication whatsoever in DeMattos et al. or in other prior art cited to use the method according to the present invention instead of the DeMattos strategy using antibodies. Accordingly, there has been no reasonable expectation of success that an apheresis method would have the effects as described in the present invention. It is, however, completely clear that the apheresis according to the present invention has completely different effect than the effects of the antibody treatment disclosed by DeMattos et al..

This is already evident by the fact that there is no increase of Aβ concentration in the patient's blood in the apheresis method according to the present invention, whereas DeMattos et al. report an increase in plasma Aβ which is obviously a prerequisite for the change in the equilibrium disclosed in DeMattos et al.. A skilled person in the art could not have expected

that an apheresis device could have such an effect so there would have been no motivation at all to try this.

Moreover, it is clear that the interaction of m266 with plasma Aβ and the detection of this interaction by the immune system is essential to the method according to DeMattos et al.. Binding of m266 to plasma Aβ appears to act as a label of plasma Aβ which enables subjection of this m266 labeled Aβ to the clearance and to the whole immune cascade following thereafter, which not only seems to trigger an increase of the expression of Aβ into plasma, but also the equilibrium change between brain and plasma Aβ. It is also evident that decrease of brain Aβ cannot be explained by a decrease in plasma Aβ (such as in the apheresis case), it seems to be the increase of plasma Aβ together with the processes involved in clearance of m266/A conjugates by the body which seem to be responsible for these processes according to DeMattos et al..

Finally, why should a skilled person in the art "after reaching new equilibrium between Aβ in the brain and blood" according to DeMattos et al. further remove Aβ from the body? Couldn't it be expected that then the "old" equilibrium would restore the Aβ deposits in the brain? Moreover, again, the present invention does not deal with further development of the new equilibrium according to DeMattos., it deals with an independent alternative to the DeMaffos strategy. It has also be mentioned that Aβ is of course not "toxic". It is a physiological protein which must have a function and which can, in certain circumstances, result in deposits in the brain which could be connected to Alzheimer's Disease.

The present invention avoids any contact of the antibody with the patient. Accordingly, severe risks such as triggering autoimmune responses (which are likely and already proven for administering antibodies against physiological proteins; in the present case clinical trials with an anti-Aβ antibodies have to be stopped due to such neuro-inflammatory processes) are prevented *ab initio*. The present invention also does not have to make use of

increased plasma Aβ levels as obtained by DeMattos et al. after m266 administration. There would have been a considerable risk that such increased Aβ plasma levels could also increase Aβ levels in the brain in humans (in contrast to the mouse model). Such risk is not taken at all with the present invention because neither is the antibody contacted with the patient nor is an antibody/A complex contacted with the immune system of the patient resulting in a clearance cascade.

In view of the above, withdrawal of both rejections applied under 35 USC 103(a) is requested.

To the provisional rejection citing copending application 11/571,970, in accordance with MPEP § 822.01, Applicants request that:

> If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Allowance of the claims is requested.

Respectfully submitted,

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